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(57) Abstract

The invention relates to polypeptides and fragments thereof, to their use in the prevention, diagnosis and treatment of auto-immune disease such as rheumatoid arthritis (RA), and to methods of preparing these fragments. Examples of such polypeptides include fragments of human heat shock protein hsp58. The invention provides a polypeptide of up to 21 amino acid residues which comprises or consists of the following sequences: (1) VGLTLENADLSL (SEQ ID 107), (2) VLNRLKVGLQV (SEQ ID 108), (3) LTLNLEDVQPHD (SEQ ID 110) or a homologue or functional equivalent or mimetic thereof. The invention provides a vaccine for the prophylactic or therapeutic treatment of RA which comprises a polypeptide as described above.

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POLYPEPTIDES AND THEIR USE IN TREATMENT AND PROPHYLAXIS OF AUTO-IMMUNE DISEASE

The present invention relates to polypeptides and fragments thereof, to their use in the prevention, diagnosis and treatment of auto-immune disease such as rheumatoid arthritis, and to methods of preparing these fragments.

Autoimmune diseases are thought to arise as a result of similarities between a foreign molecule or antigen and a molecular structure of the organism itself. Chronic forms of arthritis are thought to involve autoimmunity to constituents of the joints in particular of the connective tissues of the body.

Rheumatoid arthritis (RA) is the most common of the arthritides which exhibit autoimmune manifestations [reviewed in Elson et al, Autoimmunity (1992) 13:327]. The disease is the third most common of the elderly and causes a tremendous burden of pain and suffering. It has been known for some time that an association exists between HLA-DR4 and RA suggesting a T-cell involvement [Stasney, New Eng. J. Med. (1978) 298:869 and Watanabe et al, J. exp. Med. (1989) 169:2263] and a genetic contribution to the disease. However, recent twin studies [Silman et al, Brit. J. Rheumatol. (1993) 32:903] have suggested that the upper limit of the genetic

contribution is only 15%. It follows that the main factors contributing to the induction of RA are environmental. This contention is supported by the increased incidence of RA in South Africans as they move from villages to towns [Solomon et al, Ann, rheum. Dis. (1975) 34:128] and the increasing evidence of abnormal immune responses to microbes in patients with the disease [Deighton et al, Brit. J. Rheumatol. (1992) 31:241]. Such considerations have led to the suggestion that RA is triggered by bacterial or viral antigens which may share a high degree of homology with self protein [reviewed in reference McCulloch et al, Clin. Exp. Immunol. (1993) 92:1].

One model has proved useful in investigating environmental factors which contribute to the disease is pristane-induced arthritis (PIA). This model is based upon the finding that a proportion of mice injected intraperitoneally with the paraffin oil pristane (2, 6, 10, 14-tetramethylpentadecane) develop a chronic T-cell dependent inflammatory arthritis between 60 and 200 days later depending on the strain of mice [Potter M, J. Immunol. (1981) 127:1591, Bedwell et al, J. Immunol. (1987) 25:393, Wooley et al, Arthritis. Rheum. (1987) 32:1022, Wooley et al, Arthritis. Rheum. (1989) 32:1022 and Levitt et al, J. Rheumatol. (1992) 19:1342]. The time course of PIA thus distinguishes it from other established animal models resembling RA such as adjuvant

arthritis, streptococcal cell wall arthritis and collagen-induced arthritis. Histolopathologically the arthritis is characterised by cell infiltration and synoviocyte hyperplasia with cartilage erosions and the formation of pannus [Bedwell et al, J. Immunol. (1987) 25:393, Hopkins et al, Rheumatol. Int. (1984) 5:21 and Thompson et al, Imm. Let. (1993) 36:227].

Recent work has demonstrated that the microbial environment influences the development of PIA. Specific pathogen free (SPF) mice maintained under sterile conditions in an isolator are resistant to the development of PIA whilst the return of such animals to a conventional environment restores their susceptibility to the induction of the disease [Thompson et al, Imm. Let. (1993) 36:227]. Although the resident bowel flora differs between susceptible and refractory mice [Thompson et al, Imm. Let. (1993) 36:227], it is not known if this change affects susceptibility to the disease or indeed how exposure to microbes renders mice susceptible to the development of PIA. However, it is known that serum of mice with PIA contains raised levels of antibodies to the immunodominant mycobacterial 65kD heat shock protein (hsp65) as compared with age matched normal animals or pristane injected mice which failed to develop the disease.

It has long been recognised that heat shock proteins

(hsp's) are immunodominant antigens in a number of infectious diseases, such as tuberculosis and leishmania. These infectious diseases can have similar abnormalities as observed in RA such as raised agalactosyl-IgG levels, the organs involved and range of autoantibodies present. Since environmental factors are clearly important in RA, microbial agents and hence hsp's were implicated.

Hsps are grouped in gene families according to their molecular weight and sequence homology within individual groups. For example, hsp60 (60KD) gene family includes members hsp65 (mycobacterial) and hsp58 (mammalian).

It was found that splenic T-cells from arthritic mice proliferate more vigorously *in vitro* in response to hsp65 than T-cells from age matched normal or non-arthritic mice. Furthermore, if the mice are immunised with hsp65 in incomplete Freud's adjuvant (IFA) prior to pristane challenge, the disease will not develop [Thompson et al, Eur. J. Immunol. (1990) 20:2479 and Thompson et al, Autoimmunity, (1991) 11:89]. This protective effect is specific to hsp65 and is not induced by the E.coli equivalent GroEl or other unrelated antigens [Thompson et al, Eur. J. Immunol. (1990) 20:2479] and cannot be attributed to antigenic competition [Barker et al, Autoimmunity. (1992) 14:73]. These findings raise the possibility that mice become sensitised to hsp by exposure to microbial flora in the environment and that

this process is necessary for the induction of arthritis by pristane injection. If so, it would be predicted that there is a relationship between sensitisation to hsp65 and susceptibility to PIA. Experiments carried out by the applicants suggest that this hypothesis is correct.

One possibility which would explain how PIA could develop from such sensitisation is that pristane promotes an immune response to epitopes on microbial hsp65 which cross react with self (mammalian) hsp58 [Thompson et al, Imm. Let. (1993) 36:227 and Thompson et al, Eur. J. Immunol. (1990) 20:2479]. This suggestion gains credence from the fact that hsps are dominant antigens in the immune response to microorganisms, despite their extraordinarily high sequence conservation throughout the eukaryotic and prokaryotic kingdoms [Cohen et al, Immunol. Today, (1991) 12 105]. Thus, every microbial hsp is studded with self epitopes for any animal with an immune system. Moreover, they are normal constituents of all cells although their synthesis is increased by many different forms of cellular stress. Since hsp 58 has been detected in the joints of patients with RA [Karlsson-Parra et al, Scand. J. Immunol. (1990) 31:283] and T-cells from mice with PIA react with joint extracts [Thompson et al, Eur. J. Immunol. (1990) 20:2479] it seems reasonable to postulate that hsp58 could be a target antigen in the joints of mice developing PIA. This hypothesis may explain the paradox that both mice with PIA and animals protected from the development of arthritis by hps65 preimmunisatiOn exhibit elevated

immune responses to the 65kD mycobacterial heat shock protein. It would be expected that only mice with PIA should develop autoimmune responses to the 60kD family of hsps whereas the response of mice pre-immunised with hsp65 should be restricted to microbial specific determinants. In other words, the response elicted by immunisation with hps65 in IFA differs from that induced by sensitisation with environmental/bowel microorganisms.

T cell-mediated response to mycobacterial antigens has been implicated in the pathogenesis of inflammatory arthritis both in experimental animal models and in man. In adjuvant arthritis in rats, it has been established that the disease can be initiated by T cell clones specific for the 65-kDa mycobacterial heat-shock protein. Rats may also be protected to subsequent adjuvant arthritis induction by pre-immunisation with either a 65 KDa specific T cell line or with the hsp itself (Van Eden et al., Nature, 1988, 331:171 and Holoshitz et al., Science 1983, 219:56).

The epitope recognised by the arthritogenic T cell clone has been localized to amino acids 180-188. EP-A-322990 describes polypeptides having amino acid sequence 172-192 of a bacterial hsp 64 and their use as immunogens for inducing resistance to auto-immune disease. WO 92/04049 discloses that a peptide comprising the amino acid

sequence corresponding to positions 180-186 of the Mycobacterium tuberculosis protein hsp65 is effective in the prevention and treatment of immune-related disease such as autoimmune arthritis.

Using the PIA model, it has been found (Thompson et al. Eur. J. Immunology, 1990, 20: 2479-2484) that autoimmune reactions to an antigen which cross-reacts with hsp65 are generated in pristane-induced arthritis. Furthermore, pre-immunisation with hsp65 has been shown to protect mice from the development of pristane-induced arthritis by altering the specificity or quality of the immune response to this antigen.

On further study using the PIA model, the applicants were surprised to find that a region of the microbial protein hsp65 quite different and remote from that described in for example WO 92/04049 is effective in providing a protective response against arthritis.

In a first aspect, the present invention provides a polypeptide of up to 21 amino acid residues which comprises or consists of the sequence

VGLTLENADLSL (SEQ ID 107)

or a homologue or functional equivalent or mimetic thereof. The above described polypeptide sequence corresponds to amino acids 302-314 of microbial (mycobacterial) hsp65. The invention also provides the use of such a polypeptide in the prophylaxis or treatment of auto-immune disease such as RA.

Most of the previous work in this area has been carried out using hsp from microbial sources since there are obvious dangers in considering the administration of 'self-antigens' in the treatment of auto-immune disease in that such antigens may increase the harmful T cell response, to the detriment of the patient.

The applicants formed a view that the role of microbial hsp's in both the induction of arthritis and protection against the disease may be due to the form of antigen presentation. Depending upon this, either T_H1 cells are induced which leads to pristane induced arthritis due to determinant spreading, or T_H2 cells are induced which leads to protection due to repertoire limitation. Assuming this to be correct, the mode of application of the immunogenic agent would have a considerable effect on this. Indeed, it has been shown (Thompson et al., Immunology 1993, 79 152-157) that type II collagen (another potential joint antigen) when administered orally, lowered both the incidence and severity of pristane-induced arthritis whereas intraperitoneally administered type II collagen exacerbated both.

The applicants decided to investigate whether the human homologue of microbial hsp65, hsp58, and fragments thereof may be employed in the prophylaxis or therapy of

RA. A trans-mucosal membrane mode of administration would preferably be employed. Full sequence information in respect of human hsp58 is known for example from Jindal et al. Mol. Cell Biol. 1989, 9:2279-2283. It is therefore proposed that human hsp58 or fragments thereof are useful in the prophylaxis or treatment of RA.

Hence the present invention provides the use of human hsp58 or a fragment thereof containing or consisting of the amino acid sequence

VLNRLKVGLQV (SEQ ID 108)

or a homologue or functional equivalent or mimetic thereof in the prophylaxis or treatment of auto-immune disease such as RA; and provides novel polypeptide fragments of up to 21 amino acid residues, per se.

It is believed by analogy with work carried out using microbial hsp65; that the region of hsp58 containing amino acid residues corresponding to 261-271 of hsp65 is important for this application.

This region is a non-conserved region and is mammalian specific. This means that the region will not cross-react with the bacterial form of the protein and administered transmucosally, would induce T-cell tolerance to it and thus prevent arthritis.

Hence the present invention further provides a

polypeptide of up to 21 amino acid residues comprising or consisting of the sequence

VLNRLKVGLQV (SEQ ID 108)

or a homologue or functional equivalent or mimetic thereof.

Examples of such polypeptides include fragments of human hsp58 protein, in particular those including the amino acid residues corresponding to 271-267 of hsp65 or homologues thereof; i.e. the amino acid sequence

DVDGEALSTLVLNRLKV (SEQ ID 109)

A particularly preferred polypeptide will consist only of the amino acids VLNRLKVGLQV.

It is believed by analogy with work carried out using microbial hsp65, that the region of hsp58 containing amino acid residues corresponding to 302-314 of hsp65 is also important for this application. This region is also a non-conserved region and is mammalian specific.

The present invention further provides the use of human hsp58 fragment containing or consisting of the amino acid sequence

LTLNLEDVQPHD (SEQ ID 110)

or a homologue or functional equivalent or mimetic thereof in the prophylaxis or treatment of auto-immune disease such as RA; and provides novel polypeptide fragments of up to 21 amino acid residues, per se.

Hence the invention further provides a polypeptide of up to 21 amino acid residues comprising or consisting of the sequence

LTLNLEDVQPHD (SEQ ID 110)

or a homologue or functional equivalent or mimetic thereof.

A particularly preferred polypeptide will consist only of the amino acids

LTLNLEDVQPHD

The polypeptides of the invention have been found to have a prophylactic or therapeutic effect when applied immunogenically in the treatment of RA.

Hence the invention further provides a vaccine for the prophylactic or therapeutic treatment of RA which vaccine comprises a polypeptide as described above. For use in the treatment, the polypeptide is suitably administered in a trans-mucosal membrane manner for example, orally or nasally. Alternatively the polypeptide may be formulated as a suppository.

Administration in this way should cause the polypeptide to act in a prophylactic or therapeutic way to reduce the symptoms of RA. The mechanism by which this effect is produced is not understood. It is possible that these polypeptides act as non-specific downregulators of the immune response. The mechanism of oral tolerance has

not been fully elucidated but antigen-driven bystander suppression after oral administration of antigens has been proposed (Miller et al., J. Exp. Med. (1991) 144 791-798).

The polypeptides of the invention are suitably administered in the form of a pharmaceutical composition in combination with a pharmaceutically acceptable carrier or excipient. Such compositions form a further aspect of the invention.

Suitable carriers include solid or liquid carriers. Examples of formulations including solid carriers include tablets or suspensions for oral administration or suppositories. Suitable liquid carriers include oils or water. The compositions may be adapted for nasal administration by inhalers, atomizers or sprays as are available in the art.

In suitable circumstances it may be desirable or necessary to administer the polypeptide, or a pharmaceutical composition including the polypeptide, parenterally, for example subcutaneously, intramuscularly, intravenously or intra peritoneally.

The polypeptides of the invention can be produced using various techniques which would be apparent to the skilled person. For example, they may be obtained by

fragmentation of human hsp58 using conventional techniques after which the desired fragments obtained by purification, again using techniques which are known in the art. However peptides obtained by this method are less likely to have the precisely the desired length.

Alternatively, the polypeptides may be obtained using recombinant DNA technology. The nucleotide sequence encoding the desired polypeptide can be incorporated into a suitable host using a vector system which causes expression of the polypeptide.

Preferably however, polypeptides sequences may be generated entirely synthetically using standard chemical methods or peptide synthesizers available in the art.

As used herein, the expression 'homologue' refers to peptides having an amino acid sequence which is are at least 60%, preferably 70% and most preferably at least 80% homologous to the described polypeptide. The expression 'functional equivalent' or 'mimetic' relates to any chemical, which may be a peptide or other organic chemical which produces similar effects *in vivo* to the compounds of the present invention. In particular, such compounds will produce a protective immunogenic response against RA when applied in pristane-induced arthritis model using tests as described in the examples hereinafter.

The observations and deductions which led to the present invention will now be outlined with reference to the accompanying drawings in which:

Figure 1 is the peptide library comprising eleven pools of overlapping peptides corresponding to the entire sequence of microbial hsp65. (SEQ IDs Nos. 1-106)

Figure 2 shows a comparison of the proliferative response of T cells from each of 6 arthritic mice (top panel), 6 protected mice (middle panel) and 6 normal mice (n=6) to the eleven pools of overlapping peptides defined in Figure 1;

Figure 3 shows the results of studies to determine the protection against PIA of mice pre-immunised with microbial hsp65 polypeptides;

Figure 4 shows the entire amino acid sequence of human hsp58 (top line) in corresponding relationship to the entire sequence of microbial hsp65 (lower line);
(SEQ IDs Nos. 107-109)

Figure 5 shows the sequences and % homology of 5 peptides in the region hsp65 m 251-312 and the corresponding sequences of hsp58; (SEQ IDs Nos. 110-117)

Figure 6 shows the therapeutic effect of immunisation with polypeptides of the invention at 60 days post pristane injection (D=60); and

Figure 7 shows the prophylactic effect of pre-immunisation with polypeptides of the invention at 10 days prior to pristane injection (D=-10).

Experiment 1

Proliferation of T cells *in-vitro* from PIA mice, hsp65 protected mice and normal age-matched mice.

Animals. Male CBA/Igb mice aged between 4 and 8 weeks were used unless otherwise specified. CBA/Igb mice were obtained by back-crossing (101 strain x CBA) F1 hybrids to CBA mice and selecting those mice with Igb allotype in their serum.

Arthritis induction by pristane. One group of six mice were immunised intraperitoneally with 50 micrograms of mycobacterial hsp65 administered as an emulsion in incomplete Freuds adjuvant (IFA). This group formed the protected group of mice. After ten days, this group and a further group of 6 mice received two intraperitoneal injections of 0.5ml of pristane 50 days apart (Aldrich

Chemical Co., Milwaukee, WI.) in order to induce arthritis. A final group of 'normal' mice were maintained as controls.

Synthetic peptides used as antigens in immunisation studies. A library consisting of 106 overlapping peptides, representing the complete sequence of microbial hsp65, of between 15 and 19 amino acids in length, was synthesised using a simultaneous multiple-peptide solid phase synthetic method [Houghton R.A. Proc. Natl. Acad. Sci. USA. (1985) 82:5131] using a polyamide resin [Arshady et al, J. Chem. Soc. Perkin Trans. (1981) I.529] and FMOC chemistry. The complete library is shown in Figure 1. Completed peptides were extracted from the resin using trifluoroacetic acid and suitable scavengers, and isolated by solvent evaporation and precipitation with methanol and diethylether. Purity was checked by amino acid analysis and by HPLC. Irrelevant control antigens BSA and human IgG were also used along with the mitogen ConA.

Eleven antigens were prepared, each comprising a pool of the groups of polypeptides, set out in Figure 1 as groups 1-11.

Preparation of T-cells and APC for culture. After 200 days, spleens of individual mice were aseptically removed and single cell suspensions made in a Petri dish containing RPMI-1640 medium supplemented with 20mM HEPES (pH 7.2, Flow Labs). Erythrocytes were removed by

treating the spleen cells with 0.83% (w/v) NH4Cl solution buffered with Tris (pH 7.2). After washing, cells were suspended in RPMI-1640 HEPES at 1.25 x 10^7cells/ml. Responder T cells were enriched according to the panning method of Engleman et al [Engleman et al. J. Immunol. (1981) 127:2124]. Briefly, 10cm diameter Petri dishes (Sterilin Ltd., Hounslow, GB) were coated with 5ml of 0.5 mg/ml mouse γ-globulin in PBS at room temperature for 2 hrs. After washing once with PBS, Petri dishes were incubated with 5ml of a 1/100 dilution of rabbit anti-mouse Ig serum at 4°C overnight. After washing, 8ml of the spleen cell suspensions (1x10^8cells) were poured into the mouse Ig-rabbit anti-mouse Ig coated Petri dishes and incubated at room temperature for 40 mins. The nonadherent cells were then gently aspirated followed by washing with medium. These cells were then used as the T cell enriched fractions. A purity of .85% was achieved as assessed by anti-Thy 1.2 staining using flow cytometry (FACScan, Becton Dickinson Ltd., Oxford, GB). Normal mouse spleen cells were used as antigen presenting cells. In these experiments the APC were irradiated 1000 rads from a caesium source (Gravatom Industries, Gosport, GB).

Culture and assay of proliferation. This was carried out as described in Thompson et al., supra. The medium employed was alpha modification of Eagle's medium (alpha MEM) (Flow) supplemented with 4mM L-glutamine (Flow), 100U/ml benzyl penicillin (Glaxo Ltd., Green ford, GB),

100μg/ml streptomycin sulphate (Evans Medical Ltd., Greenford, GB), 5 x 10^{-5}M 2-mercaptoethanol (Sigma), 20 mM HEPES and 0.5% fresh normal mouse serum. The cultures consisted of 1.25 x 10^6 purified splenic T-cells plus 1.25 x 10^6 APC per ml, in a volume of 2ml in a 24 well plate (Flow) in the presence or absence of the various antigens 92.5-10μg/ml). Alternatively, some cultures were set up in a volume of 200μl in round bottom 96 well plates (Flow). All cultures were incubated at 37°C in a humidified atmosphere of 5% CO2 and 95% air.

After the periods of incubation indicated, triplicate 100microlitre samples of each of the 2 ml cultures were transferred to 96 well, round bottom culture plates (Flow) and pulsed with 2mCi of ^{3}H-Thymidine (specific activity 70-85 Ci/mMol; Amersham International Ltd., Amersham, GB) per well for 6 hours. The cells were then harvested onto glass fibre filter mats (Whatman Ltd., Maidstone, GB) using a multiple sample harvester (Skatron AS, Lier, Norway) and the ^{3}H-Thymidine incorporated into newly synthesized DNA measured using conventional liquid scintillation procedures with a LKB rackbeta counter (LKB-Wallac Ltd., Pharmacia, Uppsala, Sweden). The results are presented (Figure 2) as stimulation indices (S.I.= cpm test divided by cpm control without antigen). Positive stimulation resulted in maximal ^{3}H-Thymidine uptake of ~30,000 counts per minute.

Experiment 2

Protection of mice against PIA by immunisation with microbial Hsp65 fragments

Animals. Male CBA/Igb mice aged between 4 and 8 weeks as described in Experiment 1 were used unless otherwise specified.

Immunisation of animals. Groups of mice were immunised intraperitoneally 10 days before pristane challenge as follows:

Group	No. mice	pre-immunisation polypeptide
1	21 (6 weeks old)	-
2	21 (10 weeks old)	-
3	21	polypeptide corresponding to amino acids 302-314 of microbial hsp 65
4	15	whole microbial hsp65

50 Micrograms of each polypeptide was administered as an emulsion in IFA. The polypeptide fragment used in the pre-immunisation of group 3 was manufactured by

Cambridge Research Biochemicals of Northwich, Cheshire, UK.

Arthritis induction by pristane. Arthritis was then induced as described in Experiment 1 by two intraperitoneal injections of 0.5ml of pristane 50 days apart. The animals were examined for the incidence of arthritis in the ankle joints at various time points. The final incidence was assessed 200 days post pristane injection. The arthritis was assessed by measuring the ankle joints with a micrometer. In CBA/Ig^b mice the swollen joints ranged in size from 3.0-4.0mm compared with normal joints which had a range from 2.5-2.8mm. However, this difference could easily be distinguished, and in most experiments the joints were assessed visually, arthritis being scored at present or absent [Thompson et al, Eur. J. Immunol. (1990) 20:2479 and Barker et al, Autoimmunity. (1992) 14:73].

The percentage of animals in each group which developed arthritis after a period of 200 days is shown in Figure 3. It is clear that the peptide region corresponding to 302-314 of hsp65 generates an improved protective effect against RA in mice than when whole hsp65 is applied and confirms that this sequence, which is

VGLTLENADLSL

is effective in producing a beneficial effect.

The present inventors have shown in a co-pending application that amino acids 261-271 of microbial hsp65 can be useful in prophylaxis or treatment of auto-immune disease.

In view of the above-mentioned results it is clear that another region of microbial hsp65 which can effectively be used in an immunisation programme is that corresponding to amino acids 302-314 in the sequence. On looking at the corresponding regions of the human homologue hsp58 which, as mentioned above, is non-conserved and so will not cross-react with microbial hsp65, it appears that these will also have a useful effect, provided they can be administered in a 'safe' manner. By analogy with the work using type II collagen, it would seem that administration using a trans-mucosal membrane route, such as oral or nasal application could be appropriate.

To assist comparison between the amino acid sequence of microbial hsp65 (Figure 1) and the sequence of human hsp58, Figure 4 shows the two complete sequences in corresponding alignment, with hsp58 above hsp65. Note that the numbering of hsp65 amino acids is used herein. References herein to amino acid sequence numbers for human fragments (from hsp58) are the numbers of the corresponding hsp60 sequence region. Thus, for example, reference herein to human hsp58 region h 261-271 corresponds to microbial m 261-271 but is, in fact, amino acid 287-297 of the upper sequence of Figure 4.

Likewise, h 302-314 corresponds to m 302-314 but is, in fact, amino acids 330-341 of the upper sequence of Figure 4.

In order to highlight the non-conserved nature of the regions m 261-271 and m 302-314 in comparison to the corresponding regions of the human hsp58 sequence, Figure 5 tabulates the % homology of 5 sequences of the complete region covered by hsp65 m 251-312.

Example 1

Protection of mice against PIA by oral immunisation with human hsp58 fragment.

The eleven amino acid polypeptide of sequence VLNRLKVGLQV (h 261-271):SEQ ID 108) was prepared for use in the Example by Cambridge Research Biochemicals, Gadbrook Par, Nothwich, Cheshire, UK. This polypeptide can then be used to demonstrate the invention using the following methods.

Male CBA/Igb mice aged between 4 and 8 weeks are suitably used. Arthritis can be induced by two intraperitoneal injections of 0.5ml of pristane 50 days apart as described above. Mice which are to be subjected to an immunisation regime are given oral doses of polypeptide dissolved in saline, administered orally with

the aid of a rigid cannula inserted via the oesophagus directly into the stomach. Each animal should receive a single dose on 5 consecutive days (up to and including the day of challenge with pristane) of 50 micrograms of polypeptide.

The mice can be examined visually for the incidence of arthritis in the tarsal (ankle) joints at various time points. This may be assessed for example using a micrometer and comparing enlarged joints with normal joints. In this way, the protective effect of the polypeptide can be demonstrated.

Suitably the experiment is terminated 200 days after pristane injection. After death, stifle (knee) joints may be dissected out, fixed in neutral-buffered formalin and decalicified. If longitudinal sections are prepared and stained with haematoxylin and eosin, arthritis may be further assessed, for example by a veterinary pathologist. Suitably the assessment is carried out blind and joint changes graded according to the following system:

0. Normal.

1. Synovial hyperplasia with pannus formation and mild inflammation (polymorphonuclear leucocytes-PMN) or non-inflammatory mild articular cartilage degeneration.

2. Articular cartilage degeneration with synovial hyperplasia and pannus formation. Moderate to severe inflammation (PMN and macrophages).

3. Articular cartilage degeneration with synovial hyperplasia and pannus formation. Severe inflammation (PMN and macrophages). Significant inflammation in joint space with PMN, macrophages and debris.

In addition, a proliferative T-cell assay may be carried out as described in Experiment 1 above which will further confirm the effectiveness of this polypeptide.

Example 2

Protection of mice against PIA by nasal immunisation with human hsp65 fragment.

Example 1 may be repeated except that instead of oral administration, the polypeptide is given nasally. For this purpose, the animal is first anaesthetized and then laid on its back. A 50 microlitre drop of solution containing 50micrograms of the polypeptide described in Example 1 are then placed on the nostrils. As soon as the animal becomes conscious, the drop is rapidly inhaled. This procedure is repeated five times on five consecutive days in the same way as the oral dosing described in Example 1.

Monitoring of the animals may be carried out in the same way as described above, whereupon a protective effect is shown.

Figure 6 shows the therapeutic effect of administration of polypeptides according to the invention 60 days after first administration of pristane. 50 milligrams of peptide was administered ip as an emulsion IFA to each mouse at day 60. This was after two pristane injections, 50 days apart, one at day 0 and one at day 50. This timing is judged to be just prior to the development/onset phase of PIA. The percentage arthritis was assessed by visual scoring with the assessment being made at the 210th day (D=210). As can be seen from the figure, each of the peptides according to the invention produces a reduction in percentage arthritis in comparison to the control (IPP only).

Figure 7 shows the prophylactic effect of pre-immunisation with peptides according to the invention 10 days prior to the first pristane injection. From these results it appears that h 261-271 may actually increase the incidence of PIA whereas h 302-314 may have little or no effect in reduction of arthritis. However, m 302-314 clearly appears to give a significant reduction or nearly 4 fold in the percentage arthritis.

These data indicate that some polypeptides of the invention may be useful in prophylaxis, some may be useful in treatment, and some may have both prophylactic and therapeutic activity although not all polypeptides of the invention are expected to show both activities.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT:
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(ii) TITLE OF INVENTION: Polypeptides and their use in the Treatment and Prophylaxis of Auto-immune Disease

(iii) NUMBER OF SEQUENCES: 117

(iv) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30 (EPO)

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

Met Ala Lys Thr Ile Ala Tyr Asp Glu Glu Ala Arg Arg Gly Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

Ala Tyr Asp Glu Glu Ala Arg Arg Gly Leu Glu Arg Gly Leu Asn Ser
1 5 10 15

Leu

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

Ala Arg Arg Gly Leu Glu Arg Gly Leu Asn Ser Leu Ala Asp Ala Val
1 5 10 15

Lys

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

Glu Arg Gly Leu Asn Ser Leu Ala Asp Ala Val Lys Val Thr Leu Gly
1 5 10 15

Pro Lys Gly

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

Ser Leu Ala Asp Ala Val Lys Val Thr Leu Gly Pro Lys Gly Arg Asn
1 5 10 15

Val

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

Val Lys Val Thr Leu Gly Pro Lys Gly Arg Asn Val Val Leu Glu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

Gly Pro Lys Gly Arg Asn Val Val Leu Glu Lys Lys Trp Gly Ala
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

Asn Val Val Leu Glu Lys Lys Trp Gly Ala Pro Thr Ile Thr Asn Asp
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

Lys Lys Trp Gly Ala Pro Thr Ile Thr Asn Asp Gly Val Ser Ile
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

Pro Thr Ile Thr Asn Asp Gly Val Ser Ile Ala Lys Glu Ile Glu Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

Asp Gly Tyr Ser Ile Ala Lys Glu Ile Glu Leu Glu Asp Pro Tyr Glu
1 5 10 15

Lys

(2) INFORMATION FOR SEQ ID NO: 12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

Ala Lys Glu Ile Glu Leu Glu Asp Pro Tyr Glu Lys Ile Gly Ala Glu
1 5 10 15

Leu Val Lys

(2) INFORMATION FOR SEQ ID NO: 13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

Leu Glu Asp Pro Tyr Glu Lys Ile Gly Ala Glu Leu Val Lys Glu Val
1 5 10 15

Ala Lys

(2) INFORMATION FOR SEQ ID NO: 14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

Glu Lys Ile Gly Ala Glu Leu Val Lys Glu Val Ala Lys Lys Thr Asp
1 5 10 15

Asp Val Ala

(2) INFORMATION FOR SEQ ID NO: 15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

Glu Leu Val Lys Glu Val Ala Lys Lys Thr Asp Asp Val Ala Gly Asp
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

Val Ala Lys Lys Thr Asp Asp Val Ala Gly Asp Gly Thr Thr Thr Ala
1 5 10 15

Thr Val Leu

(2) INFORMATION FOR SEQ ID NO: 17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

Asp Asp Val Ala Gly Asp Gly Thr Thr Thr Ala Thr Val Leu Ala Gln
1 5 10 15

Ala Leu Val

(2) INFORMATION FOR SEQ ID NO: 18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18:

Asp Gly Thr Thr Thr Ala Thr Val Leu Ala Gln Ala Leu Val Lys Glu
1 5 10 15

Gly Leu

(2) INFORMATION FOR SEQ ID NO: 19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

Gln Ala Leu Val Lys Glu Gly Leu Arg Asn Val Ala Ala Gly Ala Asn
1 5 10 15

Pro Leu Gly

(2) INFORMATION FOR SEQ ID NO: 20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20:

Glu Gly Leu Arg Asn Val Ala Ala Gly Ala Asn Pro Leu Gly Leu Lys
1 5 10 15

Arg Gly

(2) INFORMATION FOR SEQ ID NO: 21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 21:

Val Ala Ala Gly Ala Asn Pro Leu Gly Leu Lys Arg Gly Ile Glu Lys
1 5 10 15

Ala

(2) INFORMATION FOR SEQ ID NO: 22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 22:

Asn Pro Leu Gly Leu Lys Arg Gly Ile Glu Lys Ala Val Asp Lys Val
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 23:

Lys Arg Gly Ile Glu Lys Ala Val Asp Lys Val Thr Glu Thr Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 24:

Lys Ala Val Asp Lys Val Thr Glu Thr Leu Leu Lys Asp Ala Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 25:

Val Thr Glu Thr Leu Leu Lys Asp Ala Lys Glu Val Glu Thr Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 26:

Leu Lys Asp Ala Lys Glu Val Glu Thr Lys Glu Gln Ile Ala Ala
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 27:

Glu Val Glu Thr Lys Glu Gln Ile Ala Ala Thr Ala Ala Ile Ser Ala
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids

(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 28:

Gln Ile Ala Ala Thr Ala Ala Ile Ser Ala Gly Asp Gln Ser Ile Gly
1 5 10 15

Asp

(2) INFORMATION FOR SEQ ID NO: 29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 29:

Thr Ala Ala Ile Ser Ala Gly Asp Gln Ser Ile Gly Asp Leu Ile
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 30:

Ala Gly Asp Gln Ser Ile Gly Asp Leu Ile Ala Glu Ala Met Asp Lys

1 5 10 15

Val Gly

(2) INFORMATION FOR SEQ ID NO: 31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 31:

Ile Gly Asp Leu Ile Ala Glu Ala Met Asp Lys Val Gly Asn Glu Gly
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 32:

Ala Glu Ala Met Asp Lys Val Gly Asn Glu Gly Val Ile Thr Val
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 33:

Lys Val Gly Asn Glu Gly Val Ile Thr Val Glu Glu Ser Asn Thr Phe
1 5 10 15

Gly Leu

(2) INFORMATION FOR SEQ ID NO: 34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 34:

Gly Val Ile Thr Val Glu Glu Ser Asn Thr Phe Gly Leu Gln Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 35:

Glu Glu Ser Asn Thr Phe Gly Leu Gln Leu Glu Leu Thr Glu Gly
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids

(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 36:

Phe Gly Leu Gln Leu Glu Leu Thr Glu Gly Met Arg Phe Asp Lys Gly
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 37:

Glu Leu Thr Glu Gly Met Arg Phe Asp Lys Gly Tyr Ile Ser Gly
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 38:

Met Arg Phe Asp Lys Gly Tyr Ile Ser Gly Tyr Phe Val Thr Asp Ala
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 39:

Gly Tyr Ile Ser Gly Tyr Phe Val Thr Asp Ala Glu Arg Gln Glu Ala
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 40:

Tyr Phe Val Thr Asp Ala Glu Arg Gln Glu Ala Val Leu Glu Glu Pro
1 5 10 15

Tyr Ile

(2) INFORMATION FOR SEQ ID NO: 41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 41:

Ala Glu Arg Gln Glu Ala Val Leu Glu Glu Pro Tyr Ile Leu Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 42:

Ala Val Leu Glu Glu Pro Tyr Ile Leu Leu Val Ser Ser Lys Val Ser
1 5 10 15

Thr Val Lys

(2) INFORMATION FOR SEQ ID NO: 43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 43:

Pro Tyr Ile Leu Leu Val Ser Ser Lys Val Ser Thr Val Lys Asp
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 44:

Val Ser Ser Lys Val Ser Thr Val Lys Asp Leu Leu Pro Leu Leu Glu
1 5 10 15

Lys Val

(2) INFORMATION FOR SEQ ID NO: 45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 45:

Ser Thr Val Lys Asp Leu Leu Pro Leu Leu Glu Lys Val Ile Gln Ala
1 5 10 15

Gly Lys

(2) INFORMATION FOR SEQ ID NO: 46:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 46:

Leu Leu Pro Leu Leu Glu Lys Val Ile Gln Ala Gly Lys Ser Leu Leu
1 5 10 15

Ile Ile Ala

(2) INFORMATION FOR SEQ ID NO: 47:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 47:

Glu Lys Val Ile Gln Ala Gly Lys Ser Leu Leu Ile Ile Ala Glu Asp
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 48:

Ala Gly Lys Ser Leu Leu Ile Ile Ala Glu Asp Val Glu Gly Glu Ala
1 5 10 15

Leu

(2) INFORMATION FOR SEQ ID NO: 49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 49:

Leu Ile Ile Ala Glu Asp Val Glu Gly Glu Ala Leu Ser Thr Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 50:

Asp Val Glu Gly Glu Ala Leu Ser Thr Leu Val Val Asn Lys Ile Arg
1 5 10 15

Gly

(2) INFORMATION FOR SEQ ID NO: 51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 51:

Val Val Asn Lys Ile Arg Gly Thr Phe Lys Ser Val Ala Val Lys Ala
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 52:

Arg Gly Thr Phe Lys Ser Val Ala Val Lys Ala Pro Gly Phe Gly Asp
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 53:

Ser Val Ala Val Lys Ala Pro Gly Phe Gly Asp Arg Arg Lys Ala Met
1 5 10 15

Leu Gln Asp

(2) INFORMATION FOR SEQ ID NO: 54:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 54:

Ala Pro Gly Phe Gly Asp Arg Arg Lys Ala Met Leu Gln Asp Met Ala
1 5 10 15

Ile

(2) INFORMATION FOR SEQ ID NO: 55:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 55:

Asp Arg Arg Lys Ala Met Leu Gln Asp Met Ala Ile Leu Thr Gly Ala
1 5 10 15

Gln Val

(2) INFORMATION FOR SEQ ID NO: 56:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 56:

Met Leu Gln Asp Met Ala Ile Leu Thr Gly Ala Gln Val Ile Ser Glu
1 5 10 15

Glu Val Gly

(2) INFORMATION FOR SEQ ID NO: 57:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 57:

Ala Ile Leu Thr Gly Ala Gln Val Ile Ser Glu Glu Val Gly Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 58:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 58:

Ala Gln Val Ile Ser Glu Glu Val Gly Leu Thr Leu Glu Asn Thr Asp
1 5 10 15

Leu

(2) INFORMATION FOR SEQ ID NO: 59:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 59:

Glu Glu Val Gly Leu Thr Leu Glu Asn Thr Asp Leu Ser Leu Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 60:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 60:

Thr Leu Glu Asn Thr Asp Leu Ser Leu Leu Gly Lys Ala Arg Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 61:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 61:

Asp Leu Ser Leu Leu Gly Lys Ala Arg Lys Val Val Met Thr Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 62:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 62:

Gly Lys Ala Arg Lys Val Val Met Thr Lys Asp Glu Thr Thr Ile Val
1 5 10 15

Glu Gly

(2) INFORMATION FOR SEQ ID NO: 63:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 63:

Val Val Met Thr Lys Asp Glu Thr Thr Ile Val Glu Gly Ala Gly
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 64:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 64:

Asp Glu Thr Thr Ile Val Glu Gly Ala Gly Asp Thr Asp Ala Ile Ala
1 5 10 15

Gly

(2) INFORMATION FOR SEQ ID NO: 65:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 65:

Val Glu Gly Ala Gly Asp Thr Asp Ala Ile Ala Gly Arg Val Ala
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 66:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 66:

Asp Thr Asp Ala Ile Ala Gly Arg Val Ala Gln Ile Arg Thr Glu Ile
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 67:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 67:

Ala Gly Arg Val Ala Gln Ile Arg Thr Glu Ile Glu Asn Ser Asp

1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 68:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 68:

Gln Ile Arg Thr Glu Ile Glu Asn Ser Asp Ser Asp Tyr Asp Arg Glu
1 5 10 15

Lys Leu

(2) INFORMATION FOR SEQ ID NO: 69:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 69:

Ile Glu Asn Ser Asp Ser Asp Tyr Asp Arg Glu Lys Leu Gln Glu Arg
1 5 10 15

Leu

(2) INFORMATION FOR SEQ ID NO: 70:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 70:

Ser Asp Tyr Asp Arg Glu Lys Leu Gln Glu Arg Leu Ala Lys Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 71:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 71:

Glu Lys Leu Gln Glu Arg Leu Ala Lys Leu Ala Gly Gly Val Ala Val
1 5 10 15

Ile Lys

(2) INFORMATION FOR SEQ ID NO: 72:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 72:

Arg Leu Ala Lys Leu Ala Gly Gly Val Ala Val Ile Lys Ala Gly
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 73:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 73:

Ala Gly Gly Val Ala Val Ile Lys Ala Gly Ala Ala Thr Glu Val
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 74:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 74:

Val Ile Lys Ala Gly Ala Ala Thr Glu Val Glu Leu Lys Glu Arg Lys
1 5 10 15

His Arg Ile

(2) INFORMATION FOR SEQ ID NO: 75:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 75:

Ala Ala Thr Glu Val Glu Leu Lys Glu Arg Lys His Arg Ile Glu Asp
1 5 10 15

Ala

(2) INFORMATION FOR SEQ ID NO: 76:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 76:

Glu Leu Lys Glu Arg Lys His Arg Ile Glu Asp Ala Val Arg Asn Ala
1 5 10 15

Lys

(2) INFORMATION FOR SEQ ID NO: 77:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 77:

Lys His Arg Ile Glu Asp Ala Val Arg Asn Ala Lys Ala Ala Val Glu
1 5 10 15

Glu Gly

(2) INFORMATION FOR SEQ ID NO: 78:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 78:

Asp Ala Val Arg Asn Ala Lys Ala Ala Val Glu Glu Gly Ile Val Ala
1 5 10 15

Gly

(2) INFORMATION FOR SEQ ID NO: 79:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 79:

Ala Lys Ala Ala Val Glu Glu Gly Ile Val Ala Gly Gly Gly Val
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 80:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 80:

Glu Glu Gly Ile Val Ala Gly Gly Gly Val Thr Leu Leu Gln Ala Ala
1 5 10 15

Pro Ala Leu

(2) INFORMATION FOR SEQ ID NO: 81:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 81:

Ala Gly Gly Gly Val Thr Leu Leu Gln Ala Ala Pro Ala Leu Asp Lys
1 5 10 15

Leu

(2) INFORMATION FOR SEQ ID NO: 82:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 82:

Thr Leu Leu Gln Ala Ala Pro Ala Leu Asp Lys Leu Lys Leu Thr Gly
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 83:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 83:

Ala Pro Ala Leu Asp Lys Leu Lys Leu Thr Gly Asp Glu Ala Thr Gly
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 84:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 84:

Lys Leu Lys Leu Thr Gly Asp Glu Ala Thr Gly Ala Asn Ile Val Lys
1 5 10 15

Val Ala

(2) INFORMATION FOR SEQ ID NO: 85:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 85:

Gly Asp Glu Ala Thr Gly Ala Asn Ile Val Lys Val Ala Leu Glu Ala

1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 86:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 86:

Gly Ala Asn Ile Val Lys Val Ala Leu Glu Ala Pro Leu Lys Gln Ile
1 5 10 15

Ala

(2) INFORMATION FOR SEQ ID NO: 87:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 87:

Lys Val Ala Leu Glu Ala Pro Leu Lys Gln Ile Ala Phe Asn Ser Gly
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 88:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 88:

Ala Pro Leu Lys Gln Ile Ala Phe Asn Ser Gly Met Glu Pro Gly Val
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 89:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 89:

Ile Ala Phe Asn Ser Gly Met Glu Pro Gly Val Val Ala Glu Lys Val
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 90:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 90:

Gly Met Glu Pro Gly Val Val Ala Glu Lys Val Arg Asn Leu Ser Val
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 91:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 91:

Val Val Ala Glu Lys Val Arg Asn Leu Ser Val Gly His Gly Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 92:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 92:

Val Arg Asn Leu Ser Val Gly His Gly Leu Asn Ala Ala Thr Gly
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 93:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 93:

Val Gly His Gly Leu Asn Ala Ala Thr Gly Glu Tyr Glu Asp Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 94:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 94:

Asn Ala Ala Thr Gly Glu Tyr Glu Asp Leu Leu Lys Ala Gly Val Ala
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 95:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 95:

Glu Tyr Glu Asp Leu Leu Lys Ala Gly Val Ala Asp Pro Val Lys Val
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 96:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 96:

Leu Lys Ala Gly Val Ala Asp Pro Val Lys Val Thr Arg Ser Ala Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 97:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 97:

Ala Asp Pro Val Lys Val Thr Arg Ser Ala Leu Gln Asn Ala Ala Ser
1 5 10 15

Ile Ala Gly

(2) INFORMATION FOR SEQ ID NO: 98:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 98:

Val Thr Arg Ser Ala Leu Gln Asn Ala Ala Ser Ile Ala Gly Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 99:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 99:

Leu Gln Asn Ala Ala Ser Ile Ala Gly Leu Phe Leu Thr Thr Glu Ala
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 100:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 100:

Ser Ile Ala Gly Leu Phe Leu Thr Thr Glu Ala Val Val Ala Asp
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 101:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 101:

Phe Leu Thr Thr Glu Ala Val Val Ala Asp Lys Pro Glu Lys Thr Ala
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 102:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 102:

Ala Val Val Ala Asp Lys Pro Glu Lys Thr Ala Ala Pro Ala Ser Asp
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 103:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 103:

Lys Pro Glu Lys Thr Ala Ala Pro Ala Ser Asp Pro Thr Gly Gly
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 104:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 104:

Ala Ala Pro Ala Ser Asp Pro Thr Gly Gly Met Gly Gly Met Asp Phe

1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 105:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 573 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 105:

Met Leu Arg Leu Pro Thr Val Phe Arg Gln Met Arg Pro Val Ser Arg
1 5 10 15

Val Leu Ala Pro His Leu Thr Arg Ala Tyr Ala Lys Asp Val Lys Phe
20 25 30

Gly Ala Asp Ala Arg Ala Leu Met Leu Gln Gly Val Asp Leu Leu Ala
35 40 45

Asp Ala Val Ala Val Thr Met Gly Pro Lys Gly Arg Thr Val Ile Ile
50 55 60

Glu Gln Ser Trp Gly Ser Pro Lys Val Thr Lys Asp Gly Val Thr Val
65 70 75 80

Ala Lys Ser Ile Asp Leu Lys Asp Lys Tyr Arg Asn Ile Gly Ala Lys
85 90 95

Leu Val Gln Asp Val Ala Asn Asn Thr Asn Glu Glu Ala Gly Asp Gly
100 105 110

Thr Thr Thr Ala Thr Val Leu Ala Arg Ser Ile Ala Lys Glu Gly Phe
115 120 125

Glu Lys Ile Ser Lys Gly Ala Asn Pro Val Glu Ile Arg Arg Gly Val
130 135 140

Met Leu Ala Val Asp Ala Val Ile Ala Glu Leu Lys Lys Gln Ser Lys
145 150 155 160

Pro Val Thr Thr Pro Glu Glu Ile Ala Gln Val Ala Thr Ile Ser Ala
165 170 175

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Asn Gly Asp Lys Glu Ile Gly Asn Ile Ile Ser Asp Ala Met Lys Lys
            180                 185                 190

Val Gly Arg Lys Gly Val Ile Thr Val Lys Asp Gly Lys Thr Leu Asn
        195                 200                 205

Asp Glu Leu Glu Ile Ile Glu Gly Met Lys Phe Asp Arg Gly Tyr Ile
    210                 215                 220

Ser Pro Tyr Phe Ile Asn Thr Ser Lys Gly Gln Lys Cys Glu Phe Gln
225                 230                 235                 240

Asp Ala Tyr Val Leu Leu Ser Glu Lys Lys Ile Ser Ser Ile Gln Ser
                245                 250                 255

Ile Val Pro Ala Leu Glu Ile Ala Asn Ala His Arg Lys Pro Leu Val
            260                 265                 270

Ile Ile Ala Glu Asp Val Asp Gly Glu Ala Leu Ser Thr Leu Val Leu
        275                 280                 285

Asn Arg Leu Lys Val Gly Leu Gln Val Val Ala Val Lys Ala Pro Gly
    290                 295                 300

Phe Gly Asp Asn Arg Lys Asn Gln Leu Lys Asp Met Ala Ile Ala Thr
305                 310                 315                 320

Gly Gly Ala Val Phe Gly Glu Glu Gly Leu Thr Leu Asn Leu Glu Asp
                325                 330                 335

Val Gln Pro His Asp Leu Gly Lys Val Gly Glu Val Ile Val Thr Lys
            340                 345                 350

Asp Asp Ala Met Leu Leu Lys Gly Lys Gly Asp Lys Ala Gln Ile Glu
        355                 360                 365

Lys Arg Ile Gln Glu Ile Ile Glu Gln Leu Asp Val Thr Thr Ser Glu
    370                 375                 380

Val Glu Lys Glu Lys Leu Asn Glu Arg Leu Ala Lys Leu Ser Asp Gly
385                 390                 395                 400

Val Ala Val Leu Lys Val Gly Gly Thr Ser Asp Val Glu Val Asn Glu
                405                 410                 415

Lys Lys Asp Arg Val Thr Asp Ala Leu Asn Ala Thr Arg Ala Ala Val
            420                 425                 430

Glu Glu Gly Ile Val Leu Gly Gly Gly Cys Ala Leu Leu Arg Cys Ile
        435                 440                 445
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Pro Ala Leu Asp Ser Leu Thr Pro Ala Asn Glu Asp Gln Lys Ile Gly
450 455 460

Ile Glu Ile Ile Lys Arg Thr Leu Lys Ile Pro Ala Met Thr Ile Ala
465 470 475 480

Lys Asn Ala Gly Val Glu Gly Ser Leu Ile Val Glu Lys Ile Met Gln
485 490 495

Ser Ser Ser Glu Val Gly Tyr Asp Ala Met Ala Gly Asp Phe Val Asn
500 505 510

Met Val Glu Lys Gly Ile Ile Asp Pro Thr Lys Val Val Arg Thr Ala
515 520 525

Leu Leu Asp Ala Ala Gly Val Ala Ser Leu Leu Thr Thr Ala Glu Val
530 535 540

Val Val Thr Glu Ile Pro Lys Glu Glu Lys Asp Pro Gly Met Gly Ala
545 550 555 560

Met Gly Gly Met Gly Gly Gly Met Gly Gly Gly Met Phe
565 570

(2) INFORMATION FOR SEQ ID NO: 106:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 544 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 106:

Met Ala Lys Thr Ile Ala Tyr Asp Glu Glu Ala Arg Arg Gly Leu Glu
1 5 10 15

Arg Gly Leu Asn Ala Leu Ala Asp Ala Val Lys Val Thr Leu Gly Pro
20 25 30

Lys Gly Arg Asn Val Val Leu Glu Lys Lys Trp Gly Ala Pro Thr Ile
35 40 45

Thr Asn Asp Gly Val Ser Ile Ala Lys Glu Ile Glu Leu Glu Asp Pro
50 55 60

Tyr Glu Lys Ile Gly Ala Glu Leu Val Lys Glu Val Ala Lys Lys Thr
65 70 75 80

Asp Asp Val Ala Gly Asp Gly Thr Thr Thr Ala Thr Val Leu Ala Gln
85 90 95

Ala Leu Val Arg Glu Gly Leu Arg Asn Val Ala Ala Gly Ala Asn Pro
100 105 110

Leu Gly Leu Lys Arg Gly Ile Glu Lys Ala Val Glu Lys Val Thr Glu
115 120 125

Thr Leu Ile Lys Gly Ala Lys Glu Val Glu Thr Lys Glu Gln Ile Ala
130 135 140

Ala Thr Ala Ala Ile Ser Ala Gly Asp Gln Ser Ile Gly Asp Ser Ile
145 150 155 160

Gly Asp Leu Ile Ala Glu Ala Met Asp Lys Val Gly Asn Glu Gly Val
165 170 175

Ile Thr Val Glu Glu Ser Asn Thr Phe Gly Leu Gln Leu Glu Ile Thr
180 185 190

Glu Gly Met Arg Phe Asp Lys Gly Tyr Ile Ser Gly Tyr Phe Val Thr
195 200 205

Asp Pro Glu Arg Gln Glu Ala Val Leu Glu Asp Pro Tyr Ile Leu Leu
210 215 220

Val Ser Ser Lys Val Ser Thr Val Lys Asp Leu Leu Pro Leu Leu Glu
225 230 235 240

Lys Val Ile Gly Ala Gly Lys Pro Leu Leu Ile Ile Ala Glu Asp Val
245 250 255

Glu Gly Glu Ala Leu Ser Thr Leu Val Val Asn Lys Ile Arg Gly Thr
260 265 270

Phe Lys Ser Val Ala Val Lys Ala Pro Gly Phe Gly Asp Arg Arg Lys
275 280 285

Ala Met Leu Gln Asp Met Ala Ile Leu Thr Gly Gly Gln Val Ile Ser
290 295 300

Glu Glu Val Gly Leu Thr Leu Glu Asn Ala Asp Leu Ser Leu Leu Gly
305 310 315 320

Lys Ala Arg Lys Val Val Val Thr Lys Asp Glu Thr Thr Ile Val Glu
325 330 335

Gly Ala Gly Asp Thr Asp Ala Ile Ala Gly Arg Val Ala Gln Ile Arg
340 345 350

Gln Glu Ile Glu Asn Ser Asp Ser Asp Tyr Asp Arg Glu Lys Leu Gln
355 360 365

Glu Arg Leu Ala Lys Leu Ala Gly Gly Val Ala Val Ile Lys Ala Gly
370 375 380

Ala Ala Thr Glu Val Glu Leu Lys Glu Arg Lys His Arg Ile Glu Asp
385 390 395 400

Ala Val Arg Asn Ala Lys Ala Ala Val Glu Glu Gly Ile Val Ala Gly
405 410 415

Gly Gly Val Thr Leu Leu Gln Ala Ala Pro Thr Leu Asp Ala Leu Lys
420 425 430

Leu Glu Gly Asp Glu Ala Thr Gly Ala Asn Ile Val Lys Val Ala Leu
435 440 445

Glu Ala Pro Leu Lys Gly Ile Ala Phe Asn Ser Gly Leu Glu Pro Gly
450 455 460

Val Val Ala Glu Lys Val Arg Asn Leu Pro Ala Gly His Gly Leu Asn
465 470 475 480

Ala Gln Thr Gly Val Tyr Glu Asp Leu Leu Ala Ala Gly Val Ala Asp
485 490 495

Pro Val Lys Val Thr Arg Ser Ala Leu Gln Asn Ala Ala Ser Ile Ala
500 505 510

Gly Leu Phe Leu Thr Thr Glu Ala Val Val Ala Asp Lys Pro Glu Lys
515 520 525

Glu Lys Ala Ser Val Pro Gly Gly Gly Asp Met Gly Gly Met Asp Phe
530 535 540

(2) INFORMATION FOR SEQ ID NO: 107:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 107:

Thr Ala Ala Pro Ala Ser Asp Pro Thr Gly Gly Met Gly Gly Met Asp
1 5 10 15

Phe

(2) INFORMATION FOR SEQ ID NO: 108:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 108:

Asp Val Glu Gly Glu Ala Leu Ser Thr Leu Val
1 5 10

(2) INFORMATION FOR SEQ ID NO: 109:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 109:

Asp Val Asp Gly Glu Ala Leu Ser Thr Leu Val
1 5 10

(2) INFORMATION FOR SEQ ID NO: 110:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 110:

Val Val Asn Lys Ile Arg Gly Thr Phe Lys Ser
1 5 10

(2) INFORMATION FOR SEQ ID NO: 111:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 111:

Phe Leu Thr Thr Glu Ala Val Val Ala Asp Lys Pro Glu Lys Thr Ala
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 112:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 112:

Val Ala Val Lys Ala Pro Gly Phe Gly Asp
1 5 10

(2) INFORMATION FOR SEQ ID NO: 113:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 113:

Arg Arg Lys Ala Met Leu Gln Asp Met Ala Ile Leu Thr Gly Gly
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 114:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 114:

Val Gly Leu Thr Leu Glu Asn Ala Asp Leu Ser Leu
1 5 10

(2) INFORMATION FOR SEQ ID NO: 115:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 115:

Leu Thr Leu Asn Leu Glu Asp Val Gln Pro His Asp
1 5 10

(2) INFORMATION FOR SEQ ID NO: 116:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 116:

Val Gly Leu Thr Leu Glu Asn Ala Asp Leu Ser Leu
1 5 10

(2) INFORMATION FOR SEQ ID NO: 117:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 117:

Leu Thr Leu Asn Leu Glu Asp Val Gln Pro His Asp
1 5 10

Claims

1. A polypeptide of up to 21 amino acid residues which comprises or consists of the sequence

VGLTLENADLSL (SEQ ID 107)

or a homologue or functional equivalent or mimetic thereof.

2. The polypeptide of claim 1 for use in prophylaxis or treatment of auto-immune disease such as rheumatoid arthritis.

3. A polypeptide of up to 21 amino acid residues comprising or consisting of the sequence

VLNRLKVGLQV (SEQ 1D 108)

or a homologue or functional equivalent or mimetic thereof.

4. Human hsp58 polypeptide or a fragment thereof containing or consisting of the amino acid sequence of claim 3 for use in the prophylaxis or treatment of auto-immune disease such as rheumatoid arthritis.

5. A polypeptide of up to 21 amino acid residues comprising or consisting of the sequence

LTLNLEDVQPHD (SEQ 1D 110)

or a homologue or functional equivalent or mimetic thereof.

6. A polypeptide according to claim 5 for use in the prophylaxis or treatment of auto-immune disease such as rheumatoid arthritis.

7. A pharmaceutical composition comprising at least one polypeptide according to any of claims 1, 3 and 5 in combination with a pharmaceutically acceptable carrier or excipient.

8. A method of prophylaxis or treatment of auto-immune disease such as rheumatoid arthritis, which method comprises administering to a patient an effective amount of a polypeptide according to any one of claims 1, 3 and 5 or a pharmaceutical compositions according to claim 7.

SEQ ID NO	SEQUENCE	GROUP
1	MAKTIAYDEEARRGL	
2	AYDEEARRGLERGLNSL	1
3	ARRGLERGLNSLADAVK	
4	ERGLNSLADAVKVTLGPKG	
5	SLADAVKVTLGPKGRNV	
6	VKVTLGPKGRNVVLEK	
7	GPKGRNVVLEKKWGA	
8	NVVLEKKWGAPTIIND	
9	KKWGAPTIINDGVSI	
10	PTIINDGVSIAKEIEL	
11	DGVSIAKEIELEDPYEK	2
12	AKEIELEDPYEKIGAELVK	
13	LEDPYEKIGAELVKEVAK	
14	EKIGAELVKEVAKKTDDVA	
15	ELVKEVAKKTDDVAGD	
16	VAKKTDDVAGDGTTTATVL	
17	DDVAGDGTTTATVLAQALV	
18	DGTTTATVLAQALVKEGL	
19	ATVLAQALVKEGLRNVAAGA	
20	QALVKEGLRNVAAGANPLG	
21	EGLRNVAAGANPLGLKRG	
22	VAAGANPLGLKRGIEKA	3
23	NPLGLKRGIEKAVDKV	
24	KRGIEKAVDKVTETL	
25	KAVDKVTETLLKDAK	
26	VTETLLKDAKEVETK	
27	LKDAKEVETKEQIAA	
28	EVETKEQIAATAAISA	
29	QIAATAAISAGDQSIGD	
30	TAAISAGDQSIGDLI	
31	AGDQSIGDLIAEAMDKVG	4
32	IGDLIAEAMDKVGNEG	
33	AEAMDKVGNEGVITV	
34	KVGNEGVITVEESNTFGL	
35	GVITVEESNTFGLQL	
36	EESNTFGLQLELTEG	
37	FGLQLELTEGMRFDKG	
38	ELTEGMRFDKGYISG	
39	MRFDKGYISGYFVTDA	
40	GYISGYFVTDAERQEA	

FIGURE 1(a)

SEQ ID NO	SEQUENCE	GROUP
41	YFVTDAERQEAVLEEPYI	5
42	AERQEAVLEEPYILL	
43	AVLEEPYILLVSSKVSTVK	
44	PYILLVSSKVSTVKD	
45	VSSKVSTVKDLLPLLEKV	
46	STVKDLLPLLEKVIQAGK	
47	LLPLLEKVIQAGKSLLIA	
48	EKVIQAGKSLLIAED	
49	AGKSLLIAEDVEGEAL	
50	LIAEDVEGEALSTL	
51	DVEGEALSTLVVNKIRG	6
52	ALSTLVVNKIRGTFKSVA	
53	VVNKIRGTFKSVAVKA	
54	RGTFKSVAVKAPGFGD	
55	SVAVKAPGFGDRRKAMLQD	
56	APGFGDRRKAMLQDMAI	
57	DRRKAMLQDMAILTGAQV	
58	MLQDMAILTGAQVISEEVG	
59	AILTGAQVISEEVGL	
60	AQVISEEVGLTLENTDL	
61	EEVGLTLENTDLSLL	7
62	TLENTDLSLLGKARK	
63	DLSLLGKARKVVMTK	
64	GKARKVVMTKDETTIVEG	
65	VVMTKDETTIVEGAG	
66	DETTIVEGAGDTDAIAG	
67	VEGAGDTDAIAGRVA	
68	DTDAIAGRVAQIRTEI	
69	AGRVAQIRTEIENSD	
70	QIRTEIENSDSDYDREKL	
71	IENSDSDYDREKLQERL	8
72	SDYDREKLQERLAKL	
73	EKLQERLAKLAGGVAVIK	
74	RLAKLAGGVAVIKAG	
75	AGGVAVIKAGAATEV	
76	VIKAGAATEVELKERKHRI	
77	AATEVELKERKHRIEDA	
78	ELKERKHRIEDAVRNAK	
79	KHRIEDAVRNAKAAVEEG	
80	DAVRNAKAAVEEGIVAG	

FIGURE 1(b)

SEQ ID NO	SEQUENCE	GROUP
81	AKAAVEEGIVAGGGV	
82	EEGIVAGGGVTLLQAAPAL	9
83	AGGGVTLLQAAPALDKL	
84	TLLQAAPALDKLKLTG	
85	APALDKLKLTGDEATG	
86	KLKLTGDEATGANTVKVA	
87	GDEATGANTVKVALEA	
88	GANTVKVALEAPLKQIA	
89	KVALEAPLKQIAFNSG	
90	APLKQIAFNSGMEPGV	
91	IAFNSGMEPGVVAEKV	
92	GMEPGVVAEKVRNLSV	
93	VVAEKVRNLSVGHGL	10
94	VRNLSVGHGLNAATG	
95	VGHGLNAATGEYEDL	
96	NAATGEYEDLLKAGVA	
97	EYEDLLKAGVADPVKV	
98	LKAGVADPVKVTRSAL	
99	ADPVKVTRSALQNAASIAG	
100	VTRSALQNAASIAGL	
101	LQNAASIAGLFLTTEA	
102	SIAGLFLTTEAVVAD	11
103	FLTTEAVVADKPEKTA	
104	AVVADKPEKTAAPASD	
105	KPEKTAAPASDPTGG	
106	AAPASDPTGGMGGMDF	

FIGURE 1(c)

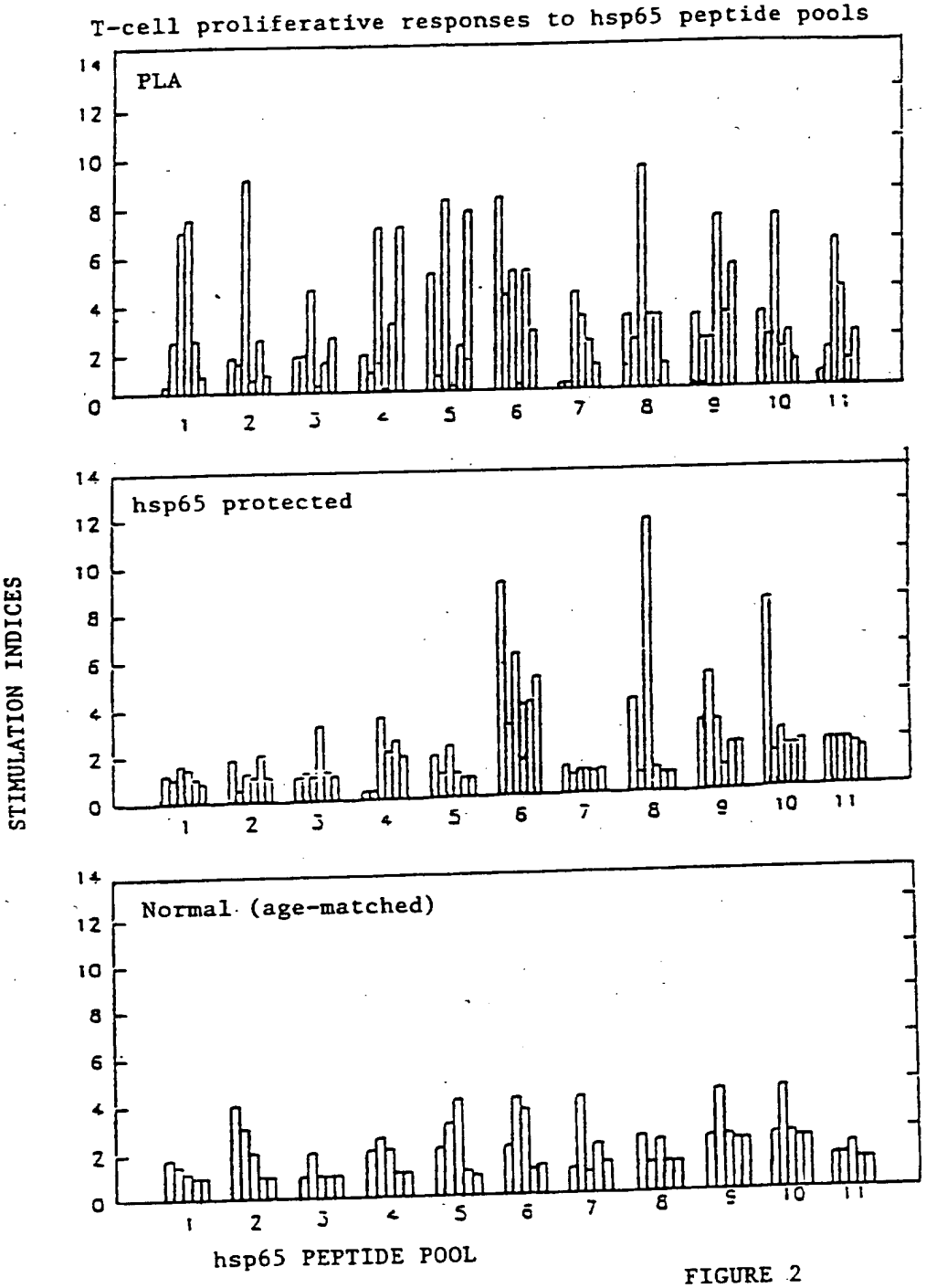
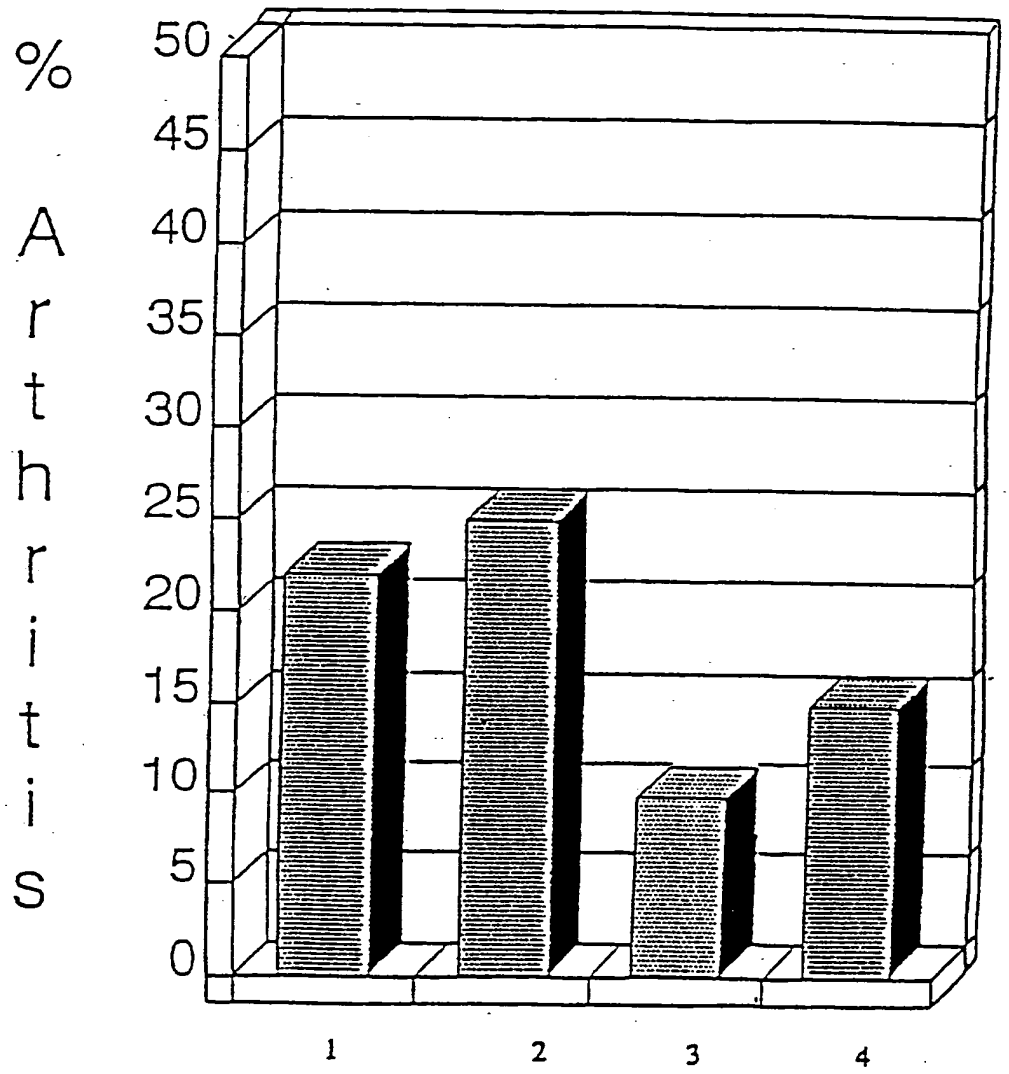


FIGURE 2

FIGURE 3



```
MLRLPTVFRQMRPVSRVLAPHLTRAYAKDVKFGADARALMLQGVDLLADAVAVTMGPKGR  60
                                ** : :  :** ::  *: :***** **:*****
                              mAKtiaydeeARrglerGlnaLADAVkVTlGPKGR  35

TVIIEQSWGSPKVTKDGVTVAKSIDLKDKYKNIGAKLVQDVANNTNEEAGDGTTTATVLA 120
:*;:*  ** * :* ***:** *:* * *  *** ** :**  *:: ***********
nVvlEKkWGaPtiTnDGVsiAKeIeLeDpYekIGAeLVkeVAkkTddvAGDGTTTATVLA  95

RSIAKEGFEKISKGANPVEIRRGVMLAVDAVIAELKKQSKPVTTPEEIAQVATISANGDK 180
  :::**:  :  ****: ::**:  **: *   * *: * * * * **  * *** **
qalvrEGlrnvaaGANPlglkRGiekAVekVtetLIKgaKeVeTkEqIAatAaISA-GDq  154

EIGNIISDAMKKVGRKGVITVKDGKTLNDELEIIEGMKFDRGYISPYFINTSKGQKCEFQ 240
 **:* :** ***  ***** :: *::  **: ***:**:**** **:     *   :
sIGdlIaeAMdKVGneGVITVeesnTfglqLEitEGMrFDkGYISgYFvtdperQeavle  214

DAYVLLSEKKISSIQSIVPALEIANAHRKPLVIIAEDVDGEALSTLVLNRLKVGLQVVAV 300
*:*:**   *:* :  ::*:** :    ***:******:********:*::: :: ***
DpYiLLvssKvStvkdllPlLEkvigagKPLlIIAEDVeGEALSTLVvNkirgtfksVAV  274

KAPGFGDNRKNQLKDMAIATGGAVFGEEGLTLNLEDVQPHDLGKVGEVIVTKDDAMLLKG 360
******* **  * ****:*** *:** ::* ** : :  ***:  *:****:  :: *
KAPGFGDrRKamLqDMAIlTGGgVisEE-vgLtLEnadlslLGKarkVvVTKDettiveG  333

KGDKAQIEKRIQEIIEQLDVTTSEVEKEKLNERLAKLSDGVAVLKVGGTSDVEVNEKKDR 420
 **   *  *:  *   :: : *:*::***:****** ****:*:*  ::**: *:* *
aGDtdaIagRvaqIrqeiensdSdYdrEKIqFRLAKLagGVAViKaGaateVElkErKhR  393

VTDALNATRAAVEEGIVLGGGCALLRCIPALDSLTPANEDQKIGIEIIKRTLKIPAMTIA 480
: **:   :*********:***  **  :* ** *  :  *   *: *:*  * :*:  **
ieDAvrnakAAVEEGIVaGGGvtLLqaaPtLDaL-klegDeatGanIvKvaLeaPlkqIA  451

KNAGVEGSLIVEKIMQSSSEVGYDAMAGDFVNMVEKGIIDPTKVVRTALLDAAGVASLLT 540
 * *:* ::::**: :      *  *  *    ::  *:::** ** *:**  **::*:*:
fNsGlEpgvvaEKvrnlpaghGlnAqtGvyedllaaGvaDPvKVtRsALqnAAsiAgLfl  512

TAEVVVTEIPKEEKDPGMGAMGGMGGGMGGGM-F 573
* *:** : *  **   :*      ** * *** *
TtEaVVadkPekEKasvpG-----GGdM-GGMdF  540
          taapasdpt---GG-M-GGMdF
```

FIGURE 4

PEPTIDES (251 - 312)

		% Homology
Myco 251-261	DVEGEALSTLV	
	* *:********	~91%
Mamm 251-261	DVDGEALSTLV	
Myco 261-271	VVNKIRGTFKS	
	* : * : : : : :	~18%
Mamm 261-271	VLNRLKVGLQV	
Myco 272 - 281	VAVKAPGFGD	
	* ** *** ****	100%
Mamm 272-281	VAVKAPGFGD	
Myco 282-296	RRKAMLQDMAILTGG	
	** * * ***: ***	75%
Mamm		
Myco 302-314	VGLTLENADLSL	
	: : * ** : :	~25%
Mamm 302-314	LTLNLEDVQPHD	

FIGURE 5

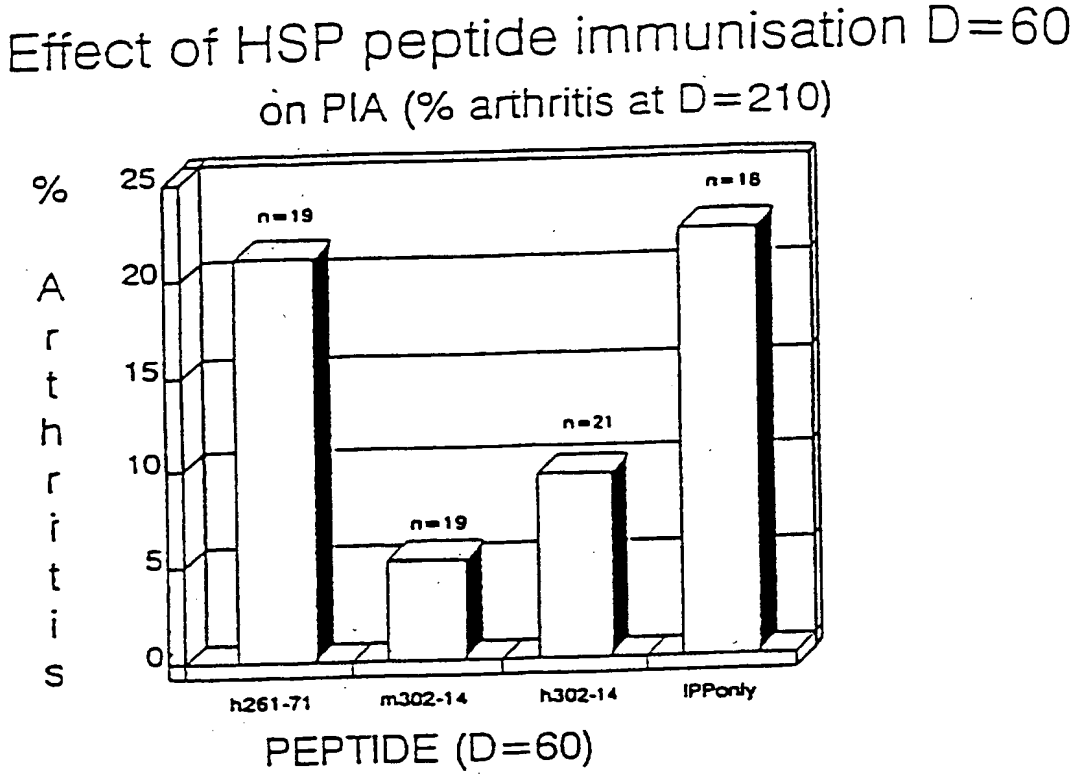


FIGURE 6

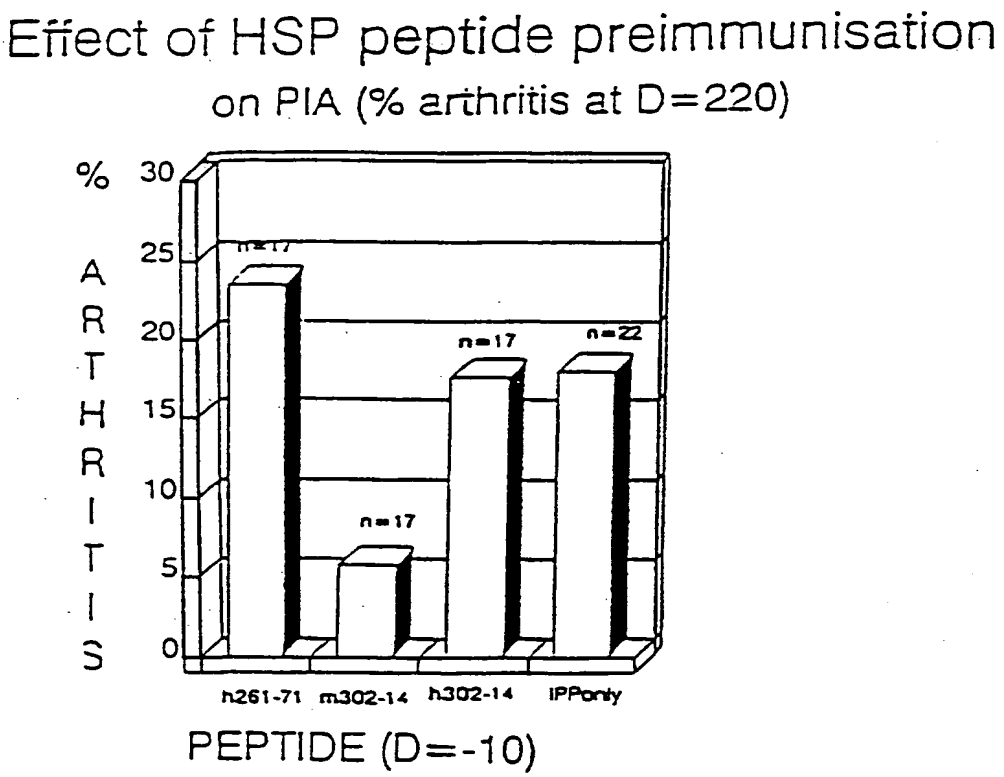


FIGURE 7

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PC1/GB 96/02382

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K14/35 C07K14/47 A61K38/17 A61K39/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 89 12455 A (WHITEHEAD INSTITUTE FOR BIOMEDICAL RESEARCH) 28 December 1989 see the whole document ---	1-8
A	WO 94 29459 A (WHITEHEAD INSTITUTE FOR BIOMEDICAL RESEARCH) 22 December 1994 see the whole document ---	1-8
P,X	WO 95 25744 A (RIJKSUNIVERSITEIT UTRECHT) 28 September 1995 see the whole document ---	1-8
P,X	WO 96 18646 A (REGENTS OF THE UNIVERSITY OF MINNESOTA) 20 June 1996 see the whole document -----	1-8

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 January 1997	12.02.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Moreau, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 96/02382

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 8
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 96/02382

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-8912455	28-12-89	AT-T-	127345	15-09-95
		CA-A-	1338778	10-12-96
		DE-D-	68924162	12-10-95
		DE-T-	68924162	25-04-96
		EP-A-	0419569	03-04-91
WO-A-9429459	22-12-94	EP-A-	0700445	13-03-96
		JP-T-	8510756	12-11-96
WO-A-9525744	28-09-95	AU-A-	1962895	09-10-95
		CA-A-	2185826	28-09-95
		EP-A-	0751957	08-01-97
WO-A-9618646	20-06-96	AU-A-	4518396	03-07-96